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SPECIAL ARTICLE

Hyperemesis Gravidrum: Updated review

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ABSTRACT

Nausea and vomiting (NV) are crucial problems during early pregnancy. Hyperemesis gravidarum (HG) is a severe form of NV. Generally, the diagnosis of HG is based on the severity of NV. We updated some criteria for HG diagnosis that have been proposed to help standardize HG research, the interesting treatable risk factors such as gastroesophageal reflux disease (GERD) or Helicobacter pylori (H. pylori) infection. Lastly, several treatment options are reviewed.

Keywords: nausea, vomiting, pregnancy, hyperemesis.

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Overview and definition

Nausea and vomiting (NV) are common conditions during early pregnancy. Pregnant women usually start experiencing NV before 5-6 weeks of gestation, and symptoms disappear around 12-16 weeks of gestation[1]. The prevalence of NV in pregnancy is estimated to be approximately 50-80% for nausea and 50% for vomiting and retching[2]. Hyperemesis gravidarum (HG) is a severe form of NV. It affects approximately 0.3-2% of all pregnancies[3]. HG have been positively reported to be associated with good fetal outcomes and strongly reduced the miscarriage risk[4]. However, severe and persistent HG can lead to adverse pregnancy outcome, such as intrauterine growth restriction, impaired maternal nutritional status and low fetal birth weight[4]. The diagnosis of HG is based primarily on the severity of NV during early pregnancy and its impact on the pregnant woman's metabolism. Currently, there are no universally accepted criteria for HG diagnosis. Some criteria for HG diagnosis have been proposed to help standardize HG research. The Fairweather criteria (1968) and the Windsor criteria (2021) are among the diagnostic criteria mentioned in the

literature[5].

The Fairweather criteria consist of[6]

- NV occurring more than 3 times /day, first appearing between 4 and 8 weeks of gestation.
- Weight loss.
- Ketonemia.
- Volume depletion.
- Electrolyte imbalance.

The Windsor criteria comprise[7]

- Mandatory features.
  - NV starting early in pregnancy (before a gestational age of 16 weeks), with at least one severe symptom.
  - Inability to drink or eat normally.
  - Strongly affects daily living activities.
- Contributory features
  - Signs of dehydration.

Etiology and risk factors of HG

HG is proposed to have a multifactorial etiology[5], including endocrine, gastrointestinal, metabolic, enzyme and immunologic adaptations during pregnancy[7]. Risk factors for HG include younger or older maternal age, abnormal pre-pregnancy weight (underweight or overweight), Black or Asian ethnicity, pregnancy with a female fetus, multiple gestations, history of pre-pregnancy gastroesophageal reflux disease (GERD) or Helicobacter pylori (H. pylori) infection[9]. The prevalence of H. pylori has been reported to be around 46% in pregnant women[10]. Interestingly, an association between H. pylori and several adverse pregnancy outcomes, such as low gestational weight gain, fetal growth restriction, and intrauterine fetal death, has been found[9-11]. Importantly, if HG worsens beyond the usual gestation period (later than 14 weeks) or if questionable abnormal clinical symptoms and signs are present, a differential diagnosis for other serious conditions should be considered. A malignant brain tumor in early pregnancy has also been reported as being mistaken for HG[12]. NV during pregnancy and HG must be distinguished from the following medical conditions[13-14]:

- Cerebral nervous system: cerebral hemorrhage, meningitis, subarachnoid hemorrhage and brain tumor.
- Ocular system: glaucoma.
- Otolaryngologic system: Meniere's disease, benign paroxysmal positional vertigo and vestibular neuritis.
- Cardiovascular system: angina pectoris, myocardial infarction.
- Female reproductive system: pelvic inflammatory disease, adnexal torsion.
- Gastrointestinal system: ulcer, appendicitis, gut obstruction, gastroenteritis, peritonitis, hepatitis, cholecystitis, cholangitis.
- Kidney and urinary bladder system: ureteral stone, pyelonephritis.
- Psychiatric problems: depression, migraine, bulimia.
- Miscellaneous: drug use.

Management of HG

Investigation

The proper investigation is arranged individually based on the clinical condition of each pregnant woman. Most investigations primarily aim to identify the causes of HG and assess its severity. Suggested investigations for HG are described below[15]:

- Complete blood count: to rule out infection, anemia.
- Serum urea and electrolytes (evaluate for hypo/hyperkalemia, hyponatremia, or high creatinine): to properly determine the type of intravenous fluid and electrolyte replacement, and to evaluate for acute kidney injury following dehydration.
- Blood glucose level: to exclude diabetic ketoacidosis in diabetic pregnant women.
- Obstetric ultrasonography: to assess fetal viability and exclude possible abnormal pregnancies associated with HG, such as multiple pregnancies or gestational trophoblastic disease.
- Urinalysis: to rule out infection. Assessing dehydration should be based on clinical signs and symptoms rather than the presence or absence of

ketonuria. Using ketonuria alone may be misleading in determining dehydration status[15]. Clinical signs and symptoms of dehydration include hypersalivation, weight loss, loss of daily activity performance or quality of life disturbances, etc.

● Other laboratory tests may be warranted in refractory cases, such as thyroid function tests, liver function tests, etc.

Treatment

A multi-modal approach to the treatment of HG has been reported. It can be categorized into the following groups:

● Antiemetic drugs (pharmaceutical modality): Antihistamines (H1 antagonists), including doxylamine combined with pyridoxine hydrochloride (vitamin B6), dimenhydrinate, meclizine and diphenhydramine, are used to relieve NV[16]. Some literature reviews have reported that only the delayed-release formulation of doxylamine succinate and pyridoxine hydrochloride is more effective than placebo in reducing NV[5,17]. Recent findings have highlighted a relationship between HG and growth/differentiation factor 15 (GDF15)[18]. Consequently, recent research has focused on the role of targeting GDF15 to reduce NV and HG. However, fetal safety is still not well-established. Future studies should investigate this further and explore screening methods to identify pregnant women at risk for HG who may need early intervention to improve clinical outcomes.

● Alternative non-pharmaceutical modality: Several interventions have been documented, such as herbs (ginger, chamomile), acupuncture and massage. The effectiveness of alternative non-pharmaceutical modalities is still controversial, and the mechanism of their therapeutic effects remains unclear[19-20].

● Dietary adjustment: A balanced and appropriate diet plays a crucial role in NV and HG control. It can help stabilize blood glucose levels and meet essential nutrient requirements. Previous studies have found that diets rich in complex carbohydrates, protein, and dietary patterns rich in fruits, vegetables, and essential vitamins and minerals can help relieve and support NV and HG management and reduce the risk of nutritional deficiencies in severe HG cases[21].

● Intravenous fluids: Rehydration, along with the correction of electrolyte imbalances, is very important.

Conclusion

In conclusion, HG is a potentially severe condition during pregnancy. Understanding the causes of HG and updating treatment options is essential.

Potential conflicts of interest

The authors declare no competing interests.

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